IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: SOLOMON2B.2

In re Application of:	)	Conf. No.: 9533
Beka SOLOMON et al.	)	Art Unit: 1649
Appln. No.: 10/749,522	)	Examiner: K. A. Ballard
Filed: January 2, 2004	)	Washington, D.C.
For: AGENTS AND COMPOSITIONS AND METHODS UTILIZING SAME USEFUL IN …	)	September 12, 2007

RESPONSE

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop Amendments
401 Dulany Street
Alexandria, VA 22314

Sir:

The present communication is responsive to the official action of April 12, 2007. Claims 1-11 and 25-34 presently appear in this case. Claims 1-6 have been withdrawn from consideration. No claim has been allowed. The Official Action of April 12, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to filamentous bacteriophage consisting of filamentous bacteriophage that displays an antibody or an antigen-binding fragment thereof. The antibody or fragment binds to an epitope of β-amyloid so as

to inhibit aggregation or cause disaggregation of β-amyloid aggregate in the subject. The filamentous bacteriophage may be part of a composition with a carrier, and, in a preferred embodiment, as an active ingredient of a pharmaceutical composition with a pharmaceutically acceptable carrier.

The examiner states that, at page 8 of applicants' response of January 16, 2007, applicants noted that a new IDS form listing the previously lined through reference had been attached to the response, but no such paper is present in the file. Applicants have been invited to resubmit this IDS form for consideration.

A copy of the IDS form referred to on page 8 of the response of January 16, 2007, is submitted herewith.

Claims 7-11 and 25-34 have been rejected under 35 U.S.C. 103 as being unpatentable over Solomon and Hanan, both as evidenced by Frenkel, and both in view of Prusiner and Pasqualini. The examiner states that Solomon and Hanan teach the inhibition and disaggregation of β-amyloid peptide by monoclonal antibodies and that Frenkel shows the specific N-terminal EFRH sequence as the specific anti-aggregating epitope. The examiner states that these references teach that a monoclonal antibody or a binding fragment thereof that binds to this anti-aggregating epitope may be used in the development of therapeutically active molecules for the treatment of diseases such as Alzheimer's disease. The examiner states that Hanan indicates that a suitable delivery system may be developed. The examiner concedes that neither Solomon nor

Hanan teach compositions comprising filamentous bacteriophage that displays an antibody or epitope binding fragment thereof. The examiner states Prusiner teaches methodologies for producing a variety of different prion protein antibodies using combinatorial phage display antibody library technology, i.e., antibodies displayed on filamentous phage. The examiner states that Prusiner teaches that combinatorial antibody library technology is advantageous over traditional hybridoma methodologies for the generation of monoclonal antibodies. The examiner states that Pasqualini teaches the targeting of specific tissues, such as brain, with phage peptide libraries and that this method may provide a new means for selective targeting of therapies. The examiner concludes that Pasqualini teaches that such technology may be used for selective tissue targeting, such as targeting of therapeutic molecules to the brain. Accordingly, the examiner concludes that the artisan would be motivated to produce a filamentous phage displaying an antibody or antigen-binding fragment directed against the anti-aggregating epitope of β-amyloid peptide for potential use in therapeutic applications. The examiner states that such a combination would be met with an expectation of success by the artisan based upon the well established methodology of expressing antibodies or antibody binding fragments on the surface of bacteriophages, as in the construction of phage display libraries. The examiner states that a statement of indended use in the preamble of a claim must be disregarded if the prior art structure is capable of performing the intended

use. The examiner states that the skilled artisan would be motivated to develop suitable delivery systems and would recognize the teachings of Prusiner and Pasqualini in this regard. The examiner states that Pasqualini evidences that a combination of a binding fragment region of an antibody and a phage would be a suitable pharmaceutical composition for *in vivo* administration and therefore would not be incongruous with either therapeutic or diagnostic use of the composition. This rejection is respectfully traversed.

The issue with respect to the present rejection is, as correctly noted by the examiner, whether it would have been obvious in the sense of 35 U.S.C. 103 to use filamentous phage as a delivery system for the epitope binding fragment of an antibody specific to an anti-aggregating epitope on β-amyloid. The most recent Supreme Court pronouncement on obviousness is *KSR International v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). Note where the Court at 1741 cited with approval the following statement from *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006):

> Rejections on obviousness grounds cannot be sustained by mere conclusary statements; instead, there must be some articulated reasoning with rational underpinning to support the legal conclusion of obviousness.

Note also where the Court stated at 1742:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.

In the present case, a person of ordinary skill in the art having common sense at the time of the invention would not have reasonably looked to Prusiner or Pasqualini to solve a problem of antibody delivery to the brain, particularly in view of the fact that neither Prusiner nor Pasqualini are related to antibody delivery. Pasqualini does not use filamentous phage as a "delivery system." Pasqualini uses the phage as a means to generate a random peptide library. He administers the phage rather than the peptides that are displayed on the phage because it would just be too difficult to remove all the peptides before administering them. Pasqualini nowhere suggests that administering the phage provides any delivery advantages. What common sense reason would one of ordinary skill in the art reading Solomon and Hanan have to take the antibody disclosed therein and specially create a phage displaying that antibody, or an epitope binding fraction thereof, solely for the purpose of using that phage as a delivery vehicle? To do so would violate the common sense of the person of ordinary skill in the art, which the Supreme Court says must be looked to when making an obviousness determination.

It is true that Pasqualini teaches that the phage displayed antibodies can get to the brain, but this does not mean that the phage is a desirable delivery system that should

be sought out when one already has an antibody, or that the phage is somehow particularly useful when attempting to deliver an antibody to the brain. Phage is used by Pasqualini by accident because he happened to use phage display technology in order to create his library of peptides. One does not need a library of peptides to practice the invention of Solomon and Hanan. One would need some other reason to put the epitope binding fragment of the antibody of Solomon and Hanan onto a phage. Pasqualini does not teach any advantage of doing so specifically for the purpose of delivering that antibody to the brain. There is nothing in Prusiner or Pasqualini that would suggest that displaying the antibody on a phage would provide any better delivery than simply administering the antibody directly. Indeed, because of the immunogenicity of the phage, one of ordinary skill in the art would consider that administering a phage-displayed antibody would be worse than administering an antibody alone (as will be discussed in greater detail below).

The reason the examiner relies on Prusiner is for its teaching that combinatorial antibody library technology is advantageous over traditional hyridoma methodologies for the generation of monoclonal antibodies. However, the antibody of the primary references has already been obtained by hybridoma technology. Why then would one want to take that antibody and

put it on a phage, as the examiner proposes in his combination of references? The only reason to do so is by a concerted hindsight reconstruction of the present invention, which the Supreme Court has warned is inappropriate.

The examiner relies on Pasqualini for the teaching that such technology may be used for selective tissue targeting, such as the targeting of therapeutic molecules to the brain. However, Pasqualini does not teach that displaying an antibody on a phage will cause selective tissue targeting to the brain. All that Pasqualini teaches is that some tiny fraction of the entire library administered finds it way to the brain and binds to brain tissue. Indeed, Pasqualini only shows that a small amount of phage goes to the brain as compared to the kidney and the liver. Those of ordinary skill in the art would expect that the phage would not pass through the blood brain barrier unless endocytosis was involved and one would not expect endocytosis in the case of an antibody. The antibody of the Solomon paper is not a receptor binding antibody. Furthermore, note the paragraph bridging the two columns of the Pasqualini paper, where it states:

> Moreover, the blood brain barrier would deter the phage.

This is further confirmation that Pasqualini actually teaches away from creating a phage displaying the epitope binding

antibody fragment of Solomon and Hanan for the purpose of delivery past the blood brain barrier.

A major part of what makes phage an excellent delivery system for the purpose of the present invention, is the discovery that intranasal administration of phage bearing an antibody allows the phage and the antibody carried thereby to bypass the blood brain barrier (see examples 7 and 8 of the present specification, beginning at paragraph 0246). Reference is also made to paragraphs [0129]-[0132] of the present specification, which explain why intranasal administration through the olfactory receptor neurons is a particularly advantageous method of getting the Aβ anti-aggregating antibodies across the blood brain barrier.

Another reason why a person of ordinary skill in the art, using common sense, would not be motivated to use phage as a delivery vehicle for an antibody is because phage is known to be immunogenic and to increase the immunogenicity of any peptide carried thereby. This is particularly true when the phage is administered iv, as is done by Pasqualini. When administering antibodies, no immunological response is desired. The present invention is not a vaccine where it is desirable to raise an immune response to a peptide; it is a delivery vehicle for antibody-binding fragments that bind to anti-aggregating epitopes of Aβ. Submitted herewith as evidence in this regard

is Delmastro et al., "Immunogenicity of Filamentous Phage Displaying Peptide Mimotopes After Oral Administration", *Vaccine*, 15:1276-1285 (1997). Note the first sentence of the discussion on page 1283 of Delmastro, where it states:

> Filamentous bacteriophages displaying foreign peptide epitopes are strongly antigenic when administered parenterally.

See also the second full paragraph and the first column on page 1284 where Delmastro states:

> It has been previously reported that filamentous phages displaying foreign peptides can be used for effective i.p. immunization in mice and rabbits without the use of adjuvants.

Thus, even without use of adjuvant, one of ordinary skill in the art would expect that administration of antibodies displayed by filamentous phage would cause an undesirable immune reaction.

Accordingly, Delmastro shows that administration of phage in mice induces an immunological response, both to the wild-type proteins of the phage and to mimotopes displayed on them. This is highly desirable when one is creating a vaccine, but is totally undesirable if the phage is used only as a delivery system. This is another reason why one of ordinary skill in the art reading Solomon and Pasqualini would not be taught that putting the antibody of Solomon on a phage would create some kind of desirable delivery system. Indeed, it

would be an undesirable delivery system and common sense would teach away from doing so. Thus, one of ordinary skill in the art would not consider using phage as a delivery system for antibody as one would expect that an immune response would ensue and one does not want an immune response to an antibody.

Furthermore, when delivering the antibody of Solomon or Hanan, one wants the antibody to go to the brain where it us active. There is no reason to believe that the use of phage will help the antibody get to the brain. Only the present invention discloses this unexpected property when filamentous phage is administered intranasally, bypassing the blood brain barrier, as discussed above.

Accordingly, while Prusiner teaches that phage display technology is advantageous for the generation of monoclonal antibodies and while Pasqualini teaches that antibodies displayed on phage can reach the brain if an entire library of phages is administered intravenously, neither suggests that phage display is any kind of a desirable delivery system. Nothing taught in Prusiner or Pasqualine would motivate one of ordinary skill in the art to take an antibody that has already been generated and display it on a phage solely for the purpose of delivery. Simply said, the examiner has not submitted the articulated reasoning with rational underpinning, which is necessary to support the legal

conclusion of obviousness required by *KSR*. Indeed, *KSR* states that factfinders may take recourse to common sense. Here, common sense would dictate quite the opposite of what the examiner is suggesting, particularly in light of the known immugenicity of filamentous bacteriophage.

For all of these reasons, the presently claimed phages and compositions would not have been obvious to one of ordinary skill in the art in the sense of 35 U.S.C. 103, reading Solomon, Hanan, Frenkel, Prusiner and Pasqualini and having knowledge of applicant's evidence, such as Delmastro. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

It is submitted that all of the claims now present in case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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